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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WEGERT, SANDRA L

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,535	MARCEL ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15-17,22 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-17,22 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Remarks/Arguments and Declaration under 37 CFR §1.132, submitted 19 April 2006, have been entered and considered. Claims 1, 15-17, 22 and 51-59 are under examination as well as the following secondary Inventions: SEQ ID NO: 2 and *impaired social activity linked to sexuality*.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

Oath

The objection to the oath/declaration for non-initialed or non-dated alterations, is *withdrawn*. Applicant submitted a newly-executed oath/declaration and made alterations to the Inventors' addresses at the time of submission.

Claim Objections -

The objection to Claim 2 because it recited non-elected inventions, as set forth at page 4 of the previous Office Action (19 August 2005), is *withdrawn.* Applicants have canceled Claim 2 (19 April 2006).

Maintained/New Objections and/or Rejections

Claim Objections -

Claim 1 and Newly-added Claim 59 are objected to for encompassing non-elected inventions (such as mental disorders not related to *impaired social activity related to sexuality*).

Appropriate correction is required.

Claim Rejections- 35 USC § 112, first paragraph-Enablement

Claims 1, 15-17, 22 and 51-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of administering the SMR1 peptide of SEQ ID NO: 2 in order to treat a mental disorder, or a disorder such as *impaired social activity linked to sexuality*. The reasons for this rejection were given in the previous Office Action (pages 5-8, 19 August 2005).

Claims 1, 15-17, 22 and 51-59 are drawn to a method of treating a mental disorder in a mammal in need thereof, by administering the short peptide of SEQ ID NO: 2 to a mammal. Dependent claims define the mental disorder specifically as *impaired social activity linked to*

sexuality. Additional claims and new claims recite several disorders of sexual behavior and several routes of drug administration.

Experiments were described in the specification in which the FG-005 peptide of SEQ ID NO: 2 was administered intravenously, at doses of 3-30μg/kg, to *normal* male rats. Data were collected on the general alertness, anxiety levels and insensitivity to pain of the treated animals. The Disclosure also described experiments in which the effect of the peptide was measured in a test of anxiety: the forced swim test (page 26, instant Specification). The most comprehensive data reported the frequency and duration of several sexual behaviors when peptide-treated male rats were presented with female rats. Treated rats slept less, were reluctant to mount a female rat initially- but had more episodes of sex subsequently- and spent more time grooming both themselves and their cage-mates (see Tables I-III, Specification). The treated male rats also mounted the female more times before ejaculation, and mounted her more often during refractory periods than untreated rats (Specification, pages 14-17).

A sufficient amount of direction or guidance is lacking in claims 1, 15-17, 22 and 51-59. The specification describes the intravenous administration of SEQ ID NO: 2 and the measurement of the duration and frequency of several rat sexual behaviors. However, nowhere in the specification is a method described that is a treatment of a mental disease including *impaired social activity linked to sexuality,* as applied to humans or other mammals. Nowhere in the instant Disclosure is a nexus described between the behaviors caused by SEQ ID NO: 2, and a well-defined disorder in human beings. Nor does current or prior literature suggest actual mental disorders that might be treated with the peptide of SEQ ID NO: 2. The applicant cites the

DSM-IV diagnostic criteria associated with a hypoactive sexual desire disorder (Response, 19 April 2006, page 7) stating that such a disorder causes marked distress. The examiner agrees with these diagnostic criteria as put forth in the DSM-IV (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, section 302.71, pages 496-497). In fact, the examiner previously made the argument that it was this *lack* of distress that was one factor demonstrating that normal male rats cannot have a mental disorder related to sexual dysfunction (19 August 2005, page 6). The applicant also discusses papers by "Yoo, et al, Benassi-Benelli et al and Islam et al" (page 7, Response). The examiner could not find the reports referred to, either in previous responses, previous Information Disclosure Statements or in the Specification.

There were no animal models presented in the instant Specification that suggest mental disorders or disorders related to sexual behavior. The Specification defines such disorders as:

"As used herein, 'impaired social activity linked to sexuality' is impairment of social relationship to a sexual partner, which can lead to impairment of occupational functioning" (Specification, paragraph 54).

Applicants insist that "one with skill in the relevant art would understand the meaning of 'impaired social activity" and 'linked to sexuality'" (Response, page 7). However, the terms must still be defined in the instant Specification, and the disorders to be treated by the SMR1 peptide must be *named*. The DSM-IV, for example, lists numerous sexual behavior disorders along with their characteristics and possible underlying mechanisms (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC,

American Psychiatric Association, 1994, section 302.71, pages 496-497). The psychiatric disorders that appear most-similar to "impaired social activity linked to sexuality," as discussed in the instant Specification, may be the genus of Hypoactive Sexual Desire Disorders. These distinctly human disorders are characterized by a decreased sexual interest that is not due to physiological factors. There is no discussion in the DSM-IV of "impaired social activity" in the context of disorders of sexual interest. The Diagnostic and Statistical Manual of Mental Disorders chapter on Sexual and Gender Identity Disorders lists 20-30 disorders and subtypes. The examiner cannot determine what disorder is being treated by the instant invention, but it is probably not well-modeled by normal rats.

In the Declaration submitted under 37 CFR § 1.132 Dr. Rougeot discusses use of the SMR1 peptide to inhibit membrane bound endopeptidases in a human renal cell line. The peptide successfully blocked the ability of endopeptidase to break down exogenously-applied substance-P (Declaration, page 5). The Declaration discusses the role of the SMR1 peptide of SEQ ID NO: 2 as an inhibitor of neutral endopeptidase in both rats and humans, stating that: "[t]he Examiner alleged that evidences would be missing showing that SMRI peptides would have activity in humans or that the human homologs of SMRI exist." However, these rather minor objections were dismissed in a prior rejection and not mentioned in the last Office Action at all (19 August 2005). The examiner agrees that there are indeed a handful of SMR1 peptides (probably 3) and that they competitively inhibit neutral endopeptidase in rats as well as humans. Such activities have been demonstrated by the inventors in peer-reviewed journals (Rougeot, et al, 2003, Proc. Natl. Acad. Sci, 100(14): 8549-8554). Likewise, it is fairly well-established that

neutral endopeptidase is a widely-distributed peptidase that breaks down a variety of hormones, vascular neuromodulators and neurotransmitter peptides (Gee, et al, 1985, Biochem., 228: 119-126).

The Response (19 April 2006) and the Declaration to some extent, imply that the mechanism of SMR1's ability to "improve [the rats'] sexual behavior" (page 8, last line) is due to the increased concentrations of Substance-P, presumably in areas of the brain responsible for such behaviors. However, not only does endopeptidase break down a variety of peptides besides Substance-P, but excess Substance-P in the brain is generally believed to be *positively* correlated with mental disorders (Kramer, et al, 1998, Science, 281: 1640-1645; Takeuchi, et al, 1988, Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 12: S157-S164).

The Response (19 April 2006) also discusses the validity of the animal model used in the inventors' experiments. There are numerous lines of evidence demonstrating that normal animals are poor models of pathologies, including the fact that there are no underlying determinants or mechanisms to correct. This was discussed at length in the last Office Action (19 August 2005). The examiner had made the point that many physiological and behavioral human conditions *can* be modeled in animals since many animal diseases are similar to those of human beings. For example, castration of both male rats and male humans results in a sharp drop in libido/sexual interest (Cormio, et al, 2005, International Journal of Impotence Research, 17: 23-26). Thus, castrated male rats are good models for several conditions in the human male characterized by low/absent androgens. The problem in the instant Application was not whether SMR1 peptide can be used with a human endopeptidase (Response, page 9), but that normal rats were used to model a human condition of abnormal sexual behavior. Newport, et al (2002, Am. J. Psychiatry,

159(8): 1265-1283, cited in the last Office Action) describes some characteristics of good animal models of human behavioral disorders, such as similar underlying mechanisms. It is the accuracy of the underlying determinants of a behavior that makes an animal model of human behavior most useful. The paper advises the most caution when discussing the use of animal models of psychiatric diseases (page 1267, second paragraph), stating: "Because the pathophysiology of mental disorders remains obscure, the homology of an animal model to a human psychiatric condition cannot be absolutely demonstrated." It can be assumed that a normal animal is a very poor model of a human behavioral condition, since it has no underlying pathophysiological determinants whatsoever.

For the reasons discussed above and previously, treatment of a mental disorder by administration of SEQ ID NO: 2 is not enabled by the instant Disclosure.

Applicants were also not enabled for additional routes of administration besides venous injection or perhaps *i.p.* or *i.m* injection. However, Applicants argue that nasal administration of small peptides may work fairly well and cite a reference in which experimenters administered peptides nasally with good results (Pontiroli, A.E., Adv. Drug Deliv. Rev, 1998, 29: 81-87). Nasal administration of small peptides could be enabled, however the arguments against oral administration of peptides (as presented previously, 19 August 2005) have not been overcome. Peptides are almost certainly *digested* when administered orally (Pontiroli, A.E., Adv. Drug Deliv. Rev, 1998, 29: 81-87, abstract). Likewise, proteases abound in many tissues (Gee, et al, 1985, Biochem., 228: 119-126). Treatment methods that are complex or not well-established, must be worked out more-or-less completely at the time of filing of a patent application.

Claiming routes of administration that have been shown to be largely ineffective with peptides, and then not describing sufficient details- such as doses, solvents, carriers, etc- indicates that significant experimentation must be undertaken to enable these methods. Routes of administration can have a dramatic effect on drug disposition, and on peptide disposition in particular (Pettit and Gombotz, 1998, TIBTECH, 16: 343-349, Table 1, for example). These examples and others illustrate that the route of administration disclosed in the instant Specification does not reasonably predict untested routes of administration.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to: a) the large quantity of experimentation required to determine how to administer the SMR1 peptide to treat a mental disorder, a behavioral disorder, impaired social activity or a sexual disorder, b) the lack of direction or guidance in the specification regarding the same, c) the lack of working examples or evidence that associate a mental disorder or sexual disorder in humans with normal rats, d) the state of the art which acknowledges the complexity of behavioral disorders, e) the importance of accurately mapping underlying mechanisms in an animal model of a human disease, f) the breadth of the claims which embrace methods of using the peptide to treat human conditions, and, g) use of untested routes of administration -undue experimentation would be required of the skilled artisan to make and use the claimed invention.

35 USC § 112, first paragraph-Written Description

Claims 1, 15-17, 22 and 51-59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The reasons for this rejection were given in the previous Office Action (pages 8-10, 19 August 2005).

Claims 1, 15-17, 22 and 51-59 are directed to methods of treating a mental disorder by administering an SMR1 peptide. Further, the claims recite treatment of impaired social activity linked to sexuality, disorders that comprise symptoms of more than one disorder, and alternative routes of administration of the polypeptide.

The specification teaches administration of a polypeptide (SEQ ID NO: 2) to normal male rats. However, the specification does not teach treatment of a mental disorder in humans, and does not disclose an animal model of a mental disorder in the current Specification. The description of experiments in which SEQ ID NO: 2 is injected into normal rats is not adequate written description of a genus of treatment methods that can be applied to humans.

Applicants have argued that "while treatment of humans is not exemplified in the disclosure, this is not required for adequate description" (Response, page 10). The examiner agrees completely that treatment of humans is not necessary for an adequate description of the invention. However, the point of the Written Description rejection (19 August 2005) was that applicants are not in possession of a method of treating any mental disorder or any sexual disorder in humans or animals, and were likewise not in possession of routes of administration of the SMR1 peptides other than those that are well-established in the art.

Claim Rejections- 35 USC § 112, second paragraph

The rejection of Claims 15 and 51 for reciting indefinite claim language is *maintained.* One skilled in the art cannot determine the metes and bounds of the claimed invention because it is not clear what the phrases "impaired social activity" and activity "linked to sexuality" mean in the context of the instant Specification. Both "impaired social activity" and activity "linked to sexuality" are poorly defined in the art, and their relationship to each other in the claims is indefinite. Furthermore, "impaired social activity linked to sexuality" disorders are poorly defined in the Specification or appear to encompass many genera of diseases and disorders, including physiological (pages 14-17). Applicants have argued (page 6, 19 April 2006) that "one skilled in the psychiatric or psychological arts would readily understand" what is meant by the disorders encompassed by the claims. However, the disorders must be named using language that is typical of one skilled in the psychiatric arts, so that it can be determined exactly which treatments are being claimed. Perhaps an example of such a disorder from the DSM-IV would help define the genus of disorders to which the applicants are referring.

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The

examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
5 July 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER